



INTERNATIONAL INFORMATION INCORPORATED

December 15, 1966

Covington and Burling
701 Union Trust Building
Washington, D. C. 20005

Subject: Financial Proposal for Legal Information Storage and Retrieval
System Proposal #6060

Gentlemen:

We are pleased to submit the following financial proposal for the development and operation of a legal Information Storage and Retrieval (IS&R) system.

The overall development and operation is divided into a two-stage program and will extend from November 16, 1966 to March 7, 1967.

1. The first phase is the initial development and processing of materials for the immediate requirements of Covington and Burling and tobacco industry counsel. This phase will begin as of November 17, 1966, when we began work pursuant to your letter of intent of November 16, 1966 and will extend to the first week in March, 1967.
2. The second phase will begin after a review and evaluation of the first phase and will be the operational stage of the program.

A minimum of 5,000 articles or documents will be entered into the system by March 7, 1967. It is estimated that the maximum number in the system at the time of full operation in March 1967, will be 10,000 accessions.

Abstracting, Indexing, Scanning and Related Services.

Since the number of documents to be entered into the system by March 1, 1967 can vary by 100%, the following method of pricing has been employed. A "time and materials" method of pricing is suggested to accommodate the uncertainties in the abstracting, indexing, and scanning program. These uncertainties in-

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clude:

1. The number of articles entered in the system on a current basis.
2. An increase or decrease in the scope of coverage of literature.
3. Additional services that may be required by Covington and Burling.

Prices:

Class 27 Labor (administrative) \$22.50/hr.

Class 37 Labor (abstracting, indexing, editing, scanning, etc.) . . 14.50/hr.

Class 47 Labor (proofreading, english editing) 10.50/hr.

The above prices include typing, flexowriting (paper-tape-preparation for computer) and general overhead.

Materials (materials that are to be used directly on project, i.e., xerox, journals, references) Cost plus
a handling charge not to exceed 20%

Travel Travel by public conveyance shall be charged at cost; travel by private conveyance shall be charged at the rate of twelve cents per mile plus tolls and parking fees; lodgings, subsistence and incidental expenses shall be charged at the rate of \$20.00 per day for overnight trips and \$12.00 per day for one-day trips.

Materials and equipment from 3M Company for microfilming \$500.00/month rental

Labor: Class 43 (Microfilming) \$ 5.30/hr.

Storage and Retrieval Service

(to be provided on subcontract to Systems Science Corporation)

Storage and retrieval services will be billed on unit rates as well as an initial fee and fixed monthly fee. These charges are as follows:

Initial charge for program set up \$2,000.00

Charge for entering abstracts to reduced machine sensible form \$1.00/document

Between November 17, 1966 and March 1, 1967 the minimum amount to be expended by Covington & Burling for storage and retrieval services is \$7,000.00; the maximum is \$12,000.00.

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From March 1, 1967 a fixed monthly fee of \$3,500.00 will be charged for the following basic services:

1. Entry of up to 150 documents per month
2. Inquiries of up to 350 per month
3. Stand by services between 8 AM and 12 Midnight Monday thru Friday. Saturday stand by will be from 8 AM to 4 PM unless prior notice is received that stand by will be required between 4 PM and Midnight. This additional service will be provided free of charge.
4. A listing of all new documents added to the system at the end of each month.
5. A cumulative list of documents contained in the system complete with abstracts to be prepared once every 6 months.

Services exceeding those included in the base rate will be billed as follows:

1. Each document to be entered in excess of 150 during any one month will be billed at a rate of \$1.00 per document.
2. Each inquiry in excess of 350 during any one month will be billed at a rate of \$1.75 per inquiry.
3. Stand by services beyond the normal hours of 8 AM and 12 Midnight Monday thru Saturday will be charged at a rate of \$6.00 per hour and will require 24 hours prior notice.

Covington & Burling and other Tobacco Industry counsel may avail themselves of the inquiry services prior to March 1, 1967 and after February 1, 1967 by paying the per unit price for each inquiry they would normally pay in excess of the normal minimum charge.

Rental of Computer Program

The Computer program will be available on a rental basis \$2,000.00/month (This is only available during operation of the total program as specified in the proposal.)

Sale of Computer Program

The computer program will be available for sale on the following basis.

1. If Systems Science Corporation is in default of their subcontract the sale price will be \$48,000.00 less 40% of the total fees paid by Covington & Burling for storage and retrieval services, but not less than \$12,000.00.

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2. If Systems Science Corporation fulfills its contractual obligation and purchase of the computer program is desired by Covington & Burling, the sale price will be \$48,000.00.

The discs containing the data will belong to Covington & Burling.

Xerox Copy Service

Xerox copies of all or any articles in the center will be charged at the following rates:

Xeroxed at the same time as will be done in the usual manner during operation \$0.10/page

Xeroxed on individual request (price includes procuring document from file) \$0.15/page

Translation Service

Articles in a foreign language that are requested to be translated will be done at 3i's commercial rate. The requests will, however, be given top priority over all other translation work.

Use of Information Retrieval Services

Use of information retrieval services will be limited to the persons included on an approved list supplied to 3i by Covington & Burling.

Answers to queries sent over TWX will be sent only to approved TWX numbers on the approved user list. Any requests to be forwarded to a TWX number not included on the list will be refused.

The approved list can be updated at anytime by forwarding a letter, signed by Covington & Burling.

Review of Overall Program and Cancellation

A review meeting will be held approximately March 7, 1967 and will include a review of the entire program as well as the pricing structure for all services.

At that time, or any subsequent time, the contract will be cancellable by Covington & Burling upon 30 days notice. If the contract is so cancelled, Covington & Burling will pay 3i \$6,000.00 per month until March 7, 1968, but 3i shall be obligated to provide its services to Covington & Burling, as requested, up to the level of \$4,000.00 per month.

Billing

3i will render monthly itemized bills for all charges provided for in this contract. Terms will be net 30 days. 3i will make its regular business records and accounts available to verify all charges upon Covington & Burling's request.

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Ongoing Operation of the IS&R System After March 7, 1967

Monthly Costs (approximate)

Class 27 labor:	80 hours @ \$22.50/hr.	1,800
Class 37 labor:	400 hours @ 14.50/hr.	5,800
Class 47 labor:	320 hours @ 10.50/hr.	3,360
Class 43 labor:	160 hours @ 5.30/hr.	848
Materials and travel		<u>1,000</u>
		12,800
Computer Fee (minimum charge)		<u>3,500</u>
		16,308

Above prices include publishing and printing 25 copies of a weekly bulletin.

Prices have been prepared on the assumption that there will be a certain percentage of overlap in the work now being prepared by 3i.

Summary of Estimated Costs

Estimated cost of all services from November 7, 1966 to March 7, 1967:

Class 27 labor:	800 hours @ \$22.50/hr.	\$ 18,000
Class 37 labor:	8000 hours @ 14.50/hr.	116,000
Class 47 labor:	800 hours @ 10.50/hr.	8,400
Class 43 labor:	800 hours @ 5.30/hr.	<u>6,500</u>
	Approximate sub total based on expected number of entries	\$153,140

Computer set up and initialization	2,000
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Charge for entering materials in machine form (maximum)	<u>12,000</u>
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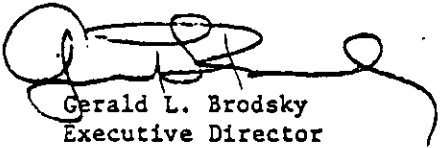
Sub total	\$ 14,000
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Grand total	\$167,140
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This proposal shall remain in effect for a period of thirty days. We sincerely hope that it meets with your requirements, and we anticipate with pleasure the opportunity of working with Covington & Burling. Your signature on the bottom of this letter will indicate your acceptance of this proposal and will be sufficient authorization for us to proceed with this work on your behalf. We look forward to hearing from you.

Very truly yours,

INTERNATIONAL INFORMATION INCORPORATED


Gerald L. Brodsky
Executive Director

GLB/rdm

APPROVED AND ACCEPTED:

COVINGTON & BURLING

By _____

Title _____

Date _____

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RELATIONSHIP BETWEEN EVOKED RESPONSE CHANGES
AND BEHAVIOR FOLLOWING SMALL DOSE OF NICOTINE
IN THE CAT

Proc. West Pharmacol. Soc. 7: 53-60, 1964

SHRYNE J.E./BROWN B.B.

Behavior and EEG responses were studied in 5 cats before and after intramuscular doses of nicotine (30-70 µg/kg). Evoked responses in the hippocampus and related structures showed that, in all but 3 of the responses studied, the excitability and responsiveness of the cats showed "a change toward awake behavior in small doses, and a change toward sleep behavior in larger doses." The three exceptions were all related. Return to normal occurred in about 90 minutes, a time which agrees with reported uptake of nicotine into the brain.

Electroencephalography (A), Nicotine pharmacology (A), Cats, Ten, Hippocampus (A), Evoked behavior response (A), Nicotine brain uptake (A), Awake behavior (A), Sleep behavior (A)/Electrode implantation (A), Fornix (A), Ventral hippocampus (A), Septum (A), "Theta" sleep (A), Dorsal hippocampus (A), Hippocampal gyrus (A), Excitability responsiveness curves (A), Behavior effects (A)/Paradoxical sleep/USA residence, English language, Los Angeles Calif residence, Sepulveda Calif residence, nicotine metabolism (A).

Calif. College of Med., Los Angeles, Calif.;
VA Hosp., Sepulveda, Calif./Calif. College of
Med., Los Angeles, Calif.; VA Hosp., Sepulveda,
Calif.

00004

MAMMALIAN DEGRADATION OF (-) DEMETHYLCOTININE .
Nature 202(4932): 594-595, .

SCHWARTZ, S. L. /MC KENNIS, H.

In the metabolism of the pyrrolidine ring of
(-)-nicotine and (-)-nornicotine (a companion
alkaloid to nicotine in many situations),
(-)-demethylcotinine is formed with a cotinine
intermediate. The details of metabolic de-
gradation of demethylcotinine are explored.
The material was obtained from the dog and fed
to male albino rats. Urine was recovered,
treated chemically and analyzed. A metabolic
sequence is suggested.

nicotine metabolism (A), nornicotine meta-
bolism (A), rats, dogs, cotinine, demethyl-
cotinine/gamma-(3-pyridyl)-gamma-methylamino-
butyric acid, 5-(3-pyridyl)-tetrahydrofuranone-
2, methyl-3-pyridylacetate, methyl-3-pyridyl-
butyrate, methyl-gamma-(3-pyridyl)-gamma-keto-
butyrate/sodium fluoride, freezing, chloroform
extraction, acetic acid eluates, paper chro-
matography/ English language, Grantor Tobacco
Ind Res Comm, Grantor Amer Tobacco Co, USA
residence, Richmond Va residence.

Med. College Virg., Richmond, Va./Med. College
Virg., Richmond, Va.

CATEGORIES FOR THE CLASSIFICATION OF MATERIALS IN THE IS&R SYSTEM

The following categories will be used to classify all materials in the system:

1. CANCER -- TOBACCO REFERENCE
2. CANCER -- NO-TOBACCO REFERENCE
3. RESPIRATORY SYSTEM (NO CANCER) -- TOBACCO REFERENCE
4. RESPIRATORY SYSTEM (NO CANCER) -- NO-TOBACCO REFERENCE
5. CARDIOVASCULAR SYSTEM (NO CANCER) -- TOBACCO REFERENCE
6. CARDIOVASCULAR SYSTEM (NO CANCER) -- NO-TOBACCO REFERENCE
7. MISCELLANEOUS -- TOBACCO REFERENCE
8. MISCELLANEOUS -- NO-TOBACCO REFERENCE
9. MEDICAL OPINION

Use of the category system results in more efficient storage and retrieval since it reduces the number of documents and descriptors to be searched.

Documents will be stored in those categories which reflect the subject matter of the article, or user interest in the article. An article may be stored either in one category or in several categories. For example, an article dealing with cancer, cardiovascular, and respiratory diseases, and mentioning tobacco, would go into categories 1, 3 and 5.

An article dealing specifically with "total mortality" but not with any individual diseases (e.g., Hammond & Horn, Part I) would be stored in category 7 in the case of a tobacco reference and in category 8 if tobacco, smoking, or nicotine were not mentioned.

Category 9, which may not be combined with any of the first 8 categories, will be used to store editorials, letters, comments to the press, or other documents expressing an opinion in the absence of a formal presentation of clinical or experimental findings.

DEFINITION OF PRIMARY, SECONDARY, TERTIARY, AND QUATERNARY DESCRIPTORS

The ANNOTATION presents, in concise form, the nature and scope of the document and its major findings, and, to the extent possible in less than 100 words, related material as follows: major opinions, major concessions, major beneficial effects, Helpful Information, and major conclusions found in the document.

The ABSTRACT is an informative, user-oriented, presentation of the purposes, methods, findings, opinions, and conclusions in the document. It is designed to amplify and supplement the ANNOTATION. It therefore presents significant results and conclusions, with emphasis on any concessions, beneficial effects, Helpful Information, and any data relating to the needs of the user, not contained in the ANNOTATION.

PRIMARY DESCRIPTORS reflect fully the ANNOTATION and title (where pertinent) of the article, and reflect only these.

SECONDARY DESCRIPTORS reflect fully the ABSTRACT only and relate to the author's methods, results, opinions, concessions, conclusions, and to beneficial effects and Helpful Information, that were not of sufficient importance to require PRIMARY DESCRIPTORS.

TERTIARY DESCRIPTORS refer to physical effects and clinical observations in relation to tobacco and non-tobacco use which do not appear in either the ANNOTATION or the ABSTRACT. When the author reports physical effects or clinical observations using such modifying terms as "increased", "decreased", "unchanged", "normal", or "abnormal", descriptors will be so modified to reflect the corresponding concepts. Descriptors will not be modified when the author gives no interpretation to reported values. All other data presented without discussion or interpretation will also be given TERTIARY DESCRIPTORS.

QUATERNARY DESCRIPTORS refer to subject matter mentioned by the author with no data or with data providing no user-oriented amplification; this includes geographic references. The country of residence of the senior author and the language of original publication will also appear in this column. If a document is simultaneously published in more than one language, of which one is the English language, the article will be indexed as "English language". The findings of other authors to which an author refers with a bibliographic citation will not be indexed; instead, the relevant referenced articles will themselves be included in the system.

DEFINITION OF DESCRIPTORS AND DESCRIPTOR COMPONENTS

- Male data - this indicates the presence of male numerical information
- Female data - this indicates the presence of female numerical information
- Male-female data - this indicates the presence of male and female numerical information
- Sex differences - this is a general term used for articles discussing sex differences, in whole or in part, and not presenting a mere quantitative ratio
- Number descriptors - The number of cases, subjects, or animals in the study will be indicated by:
- one
- ten -- for numbers up to 10 and more than one
- twenty-five - for numbers up to 25 and more than 10
- fifty - for numbers up to 50 and more than 25
- hundred - for numbers up to 100 and more than 50
- thousand - for numbers up to 1,000 and more than 100
- ten thousand - for numbers up to 10,000 and more than 1,000
- ten thousand plus - for numbers higher than 10,000
- (A) - the A in parentheses, used only in conjunction with another descriptor, indicates a finding in an experimental animal, as opposed to a human finding for which the descriptor is unmodified.
- (C) - the C in parentheses following a descriptor indicates documents dealing with the chemical composition, structure, and properties of tobacco, its smoke or components, tobacco tars, and other studies not containing biological information.

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- Dose response - this refers to the relationship, in the author's opinion, between the dose administered and the effect obtained; this will be modified by either "positive", when a positive relationship exists, or "negative", if the relationship was lacking or negative.
- Smoking amount - this term, often found in conjunction with "smoking duration", refers to the number of packs per day or a similar quantitative measure, including modifiers such as "heavy" or "light".
- Etiology - this term will not be used, being replaced by "causation".
- Beneficial effect - this term is understood to refer to a beneficial effect of tobacco use, and pertains to the information which should always be given at the end of each abstract, if present.
- Adverse effect - this term will not be used, but will appear in the Thesaurus followed by all of the adverse effects present in the system.
- Concession - this term, which is always a modifying term, can be distinguished from a statement of negative opinion or Helpful Information in that the author is admitting to a deficiency in his previously expressed positive opinion, i.e., more or less adhering to the positive view of causation or carcinogenicity but admitting that more work is needed, or that animal findings are not directly applicable to man, etc.
- HI - this is used after another descriptor and stands for helpful statement or Helpful Information; this means that a statement or point might be useful for advocacy.
- Association
Nonassociation - these terms will be used when the document refers to the presence or absence of a statistical relationship between the occurrence of two variables.

Causation 1

- this indicates a definite expression of opinion that an agent named causes, to some degree, the disease listed; this term can be followed by NPB, which stands for "no proof but" and is used to show that the author expressed an opinion in the admitted absence of evidence.

Causation 2

- this term incorporates the previous concepts of "causation suggested" and "causation unknown", and indicates that the author either feels that the causation of the disease is still unknown, fails to come to any conclusion about the causation of the disease, or makes only inconclusive statements such as that a causal relationship is suggested.

Causation 3

- this indicates a definite expression of opinion that the agent named plays no significant role in the causation of the disease.

PROJECT TIC		ACCESSION NUMBER			
TITLE: A STUDY OF TOBACCO CARCINOGENESIS. I. THE PRIMARY FRACTIONS					
AUTHOR(S): Wynder, E. L./Wright, G.					
SOURCE: Cancer 10(2): 255-271, 1957					
AFFILIATION: Sloan-Kettering Inst Cancer Res, Div Prev Med, N.Y./U Toronto, Canada					
<p>ANNOTATION: Both papillomas and carcinomas were obtained when various fractions of cigarette tar, obtained by chemical fractionation, molecular distillation, and ion exchange experiments, were applied 3 times weekly to the shaved backs of mice. In further work, the activity of various chromatographic eluates of the neutral fraction was compared, as was that of the neutral fractions from extracts of unsmoked cigarette tobacco, cigarette tobacco smoked in pipes, and cigarettes smoked by machine in the usual way. Preliminary work was also done with rabbits. While admitting that proof that "tobacco smoking causes cancer in man" "can come only from combined statistical, clinical, and epidemiological studies on man," the authors conclude that cigarette tar "is carcinogenic to mouse skin" and that "the majority, though not all, of the carcinogens are in the neutral tar fraction".</p>					
<p>ABSTRACT: King-size cigarettes manufactured in the United States were smoked 150 at a time in a machine with a mean puff volume of 35 ml. One-thousand cigarettes yielded 42 g of a cold-trapped tar with a nicotine content of 5.3%. The high toxicity due to nicotine led to its removal (along with other alkaloids) from some of the test preparations using silicotungstic acid. Whole tar and its various fractions were applied to CAF₁ and Swiss mice in 50% acetone solution, and the animals were observed for up to 24 months. The methylene-insoluble fraction produced no lesions in the more resistant CAF₁ mice and 1 carcinoma plus 2 papillomas in the Swiss mice. Survival with the use of a water-soluble fraction was good and no tumors were produced in either strain. With the acidic plus the neutral fraction, survival was good and cancers developed in 13% and 22% of the CAF₁ and Swiss mice, resp.; the nicotine-free basic fraction plus the neutral fraction led to cancers in 17% and 37%, resp.; there were generally fewer survivors among Swiss mice than among CAF₁ mice. Taken separately, the acidic and nicotine-free basic fractions produced no lesions in Swiss mice and 7% cancers in CAF₁ mice. The nicotine-free basic fraction, however, produced the most ulceration, hair loss, and hyperplasia, and further study of this fraction is suggested for the possible presence of non-hydrocarbon carcinogens. At the same time, the role of general toxicity and weight loss in carcinogenesis experiments is emphasized. Results with nicotine-free whole tar and recombined whole tar were generally the same as with untreated whole tar. When neutral tar was chromatogrammed on a silica gel column, papillomas were produced with both the hexane and CCl₄ eluates, but carcinomas only with the latter; benzene, chloroform, and methanol-pyridine eluates produced no tumors. In groups of 10 CAF₁ mice each,</p>					
ABSTRACTOR	DATE	EDITOR	PROOFREAD	FINAL OK	PREPARE DESCRIPTORS ON BACK SIDE OF THIS PAPER

Category 1

Primary descriptors	Secondary descriptors	Tertiary descriptors	Quaternary descriptors
CANCER TOBACCO CAUSATION 2	CANCER SMOKING ASSOCIATION	SMOKING MACHINE	USA RESIDENCE
TOBACCO TAR PRIMARY FRACTIONS	CANCER TOBACCO CHEMING NONASSOCIATION	CHLOROPHORM EXTRACTS	ENGLISH LANGUAGE
CIGARETTE TAR	TOBACCO CHEMING HI	SULFURIC ACID EXTRACTION	NEW YORK CITY
CIGARETTE TAR CARCINOGENICITY (A)	PUFF VOLUME	SODIUM CARBONATE EXTRACTION	TORONTO
NICE	CAF ₁ MICE	BENZOPYRENE EXTRACTION	GRANTOR AMERICAN CANCER SOCIETY
RABBITS	SWISS MICE	ACETONE EXTRACTION	LUNG CANCER SMOKING ASSOCIATION
SKIN PAINTING (A)	CIGARETTE TAR NICOTINE FREE FRACTIONS	PETROLEUM ETHER EXTRACTS	ORAL CAVITY CANCER SMOKING ASSOCIATION
SKIN CARCINOMA (A)	PIPE TOBACCO	VACUUM DISTILLATION	LARYNX CANCER SMOKING ASSOCIATION
SKIN PAPILLOMA (A)	TOBACCO BURNING TEMPERATURE	CIGARETTE MOISTURE CONTENT	CIGARETTE CONDITIONING
CIGARETTE TOBACCO	TOBACCO TAR ACIDIC FRACTION	BUTT LENGTH	PRESSURE DROP
PIPE SMOKING	TOBACCO TAR BASIC FRACTION	PUFF FREQUENCY	AMINES
ION EXCHANGE TREATMENT	KING SIZE CIGARETTES	PUFF DURATION	AROMATIC CARBOXYLIC ACIDS
COLUMN CHROMATOGRAPHY	TOBACCO TAR CHEMICAL COMPOSITION	SPECIES DIFFERENCES	ALIPHATIC CARBOXYLIC ACIDS
TOBACCO TAR NEUTRAL FRACTION	CIGARETTE TAR FRACTION COCARCINOGENICITY	ETHYLACETATE ELUATES	PHENOLS
MOLECULAR DISTILLATION	LATENT PERIOD		CRESOLS
TOBACCO TAR FRACTIONATION	TOBACCO TAR BENZOPYRENE CONTENT		XYLENEOL
TOBACCO TAR CARCINOGEN CONTENT	CIGARETTE FILTERS		TERPENES
TOBACCO EXTRACTS	SKIN ULCERATION (A)		PALMITIC ACID
ANIMAL CONCESSIONS	SKIN HYPERPLASIA (A)		OLEIC ACID
	ALOPECIA (A)		UNSATURATED FATTY ACIDS
	WEIGHT LOSS (A)		SATURATED FATTY ACIDS
	TOBACCO PYROLYSIS		PETHENOIC ACID
	HENTRIACONTANE NONCARCINOGENICITY (A)		SATURATED FATTY ACID ESTERS
	TOBACCO CUT		AROMATIC POLYCYCLIC HYDROCARBONS
	TOBACCO HENTRIACONTANE CONTENT		NAPHTHALENES
	TOBACCO TAR YIELD		ANTHRACENE
	TOBACCO TAR WATER SOLUBLE FRACTION		ALKYLANTHRACENES
	TOBACCO TAR NICOTINE CONTENT		PYRENE
	NICOTINE REMOVAL		ALKYL PYRENES
	NICOTINE TOXICITY (A)		FLUORANTHENE
	SILICOTUNGSTIC ACID		CERYSENE
	ACETONE SOLUTION		ULTRAVIOLET SPECTROSCOPY
	SILICA GEL COLUMN		FLUORESCENCE SPECTROSCOPY
	HEXANE ELUATES		ACENAPHTHYLENE
	PYRIDINE ELUATES		ALIPHATIC TRIGLYCERIDES
	CARBON TETRACHLORIDE ELUATES		PHYTOSTEROLS
	BENZENE ELUATES		STIGMASTEROL
	METHANOL ELUATES		COSMARIN
	METHANOL EXTRACTS		THIOUREA
	METHYLENE CHLORIDE EXTRACTS		TRINITROFLUORENONE
			POLYCYCLIC DEGRADATION
			SULFONATED POLYSTYRENE RESIN
			BASIC QUATERNARY AMMONIUM RESIN
			CIGARETTE PAPER
			OXYGEN SUPPLY
			SONULET EXTRACTOR
			GERANIOL
			ELEUENT POLARITY
			HYDROXY-3,4-BENZOPYRENE
			2,3,6,7-DIBENZOPHENANTHRENE
			1,2,3,4-DIBENZOPYRENE
			3,4,6,9-DIBENZOPYRENE
			1,2-BENZONAPHTHACENE
			1,2,7,8-DIBENZONAPHTHACENE

3 of 6 molecular distillate cuts of the neutral fraction led to cancers in 1 or 2 mice. In both strains of mice, the 2-propanol-insoluble ion-exchange fractions were more carcinogenic than the 2-propanol-soluble acidic and neutral fractions. In both strains again, neutral tar obtained from cigarette tobacco smoked in pipes was about twice as active (and the latent period was shorter) as that obtained from cigarette tobacco in the usual manner. This is believed to be related to the fact that the peak burning temperature in cigarettes is $884^{\circ}\text{C} \pm 30$ during a puff and $835^{\circ}\text{C} \pm 30$ between puffs, compared to $750\text{--}950^{\circ}\text{C}$ when cigarette tobacco is burned in pipes (this is 150°C higher than the peak burning temperature for pipe tobacco, and is presumably related to the cut of the tobacco used). A methanol extract of the same cigarette tobacco (unsmoked) produced 11 papillomas among 40 CAF₁ mice and 3 among 40 Swiss mice; although 1 of the latter developed into a cancer, this indicates less activity in extracts of unsmoked tobacco than in tobacco combustion products, and may help to explain the lower rate of human cancer associated with tobacco chewing. Hentriacontane, for example, which is the main paraffinic hydrocarbon in tobacco, is noncarcinogenic per se but yields a spectrum of carcinogens on pyrolysis. The authors conclude that the main effect of the nicotine-free basic fraction, which "is but slightly carcinogenic", "seems to be that of a cocarcinogen". They note that the active carcinogenic fraction which has been isolated from the neutral fraction represents only 1.5% of the total tar, and that the "benzpyrene content of the total tar as well as of the active fractions is far too low to account for the positive results. So far, no carcinogens have been identified in large enough quantity in tobacco tar or its fractions to account for the observed activity. While a summation effect of several substances remains a possibility, it is more likely that carcinogens not yet identified may be the most important ones in tobacco tar". Among the practical measures suggested on the basis of these findings are a reduction in the amounts of possible carcinogen precursors in raw tobacco, and the development of effective filters to reduce the total amounts of tar and nicotine passing through a cigarette. "Preliminary data indicate that this would effect a dilution of tar exposure, which will significantly affect the yield and latent period for tumor growth in the experimental animal....". The authors also raise the question of "what bearing, if any, experimental research in cancer has on the human cancer problem". They note that "the purpose of this investigation has not been to prove that tobacco smoking causes cancer in man". In view of the relationship between tobacco and several types of human cancer, "the present investigation was initiated to determine the specific carcinogenic substances in tobacco. It remains to be established whether such factors, once found, are also responsible for cancer formation in man. If an agent is found to be carcinogenic to a variety of animals, and if the human epidemiological data are not inconsistent with this finding, then the burden of proof lies upon those who claim that these substances are not carcinogenic to man". [Support from the American Cancer Society]

PROJ					ACCESSION NUMBER
TITLE: Etiology by Edict					
AUTHOR(S): Langston, H. T.					
SOURCE: J Thorac Cardio Surg 51:459-460, 1966					
AFFILIATION: None					
<p>ANNOTATION: In a brief editorial dealing with the 1964 Surgeon General's Report, it is noted that the conclusions reached in this report were drawn from statistical analyses and associations based on population surveys, "ignoring the clinical facets of lung cancer almost totally." A number of apparent inconsistencies between these conclusions and certain facts about lung cancer are pointed out, and the comment is made that "it seems odd that a governmental agency should so assiduously undertake to hobble a business that contributes some two billion dollars in yearly taxes without better proof of its stand."</p>					
<p>ABSTRACT: The author notes that, although the Surgeon General's Report implicates cigarette smoking as a causative factor in a large number of disease entities, life expectancy has increased rather than decreased since the discovery of tobacco. Furthermore, findings suggesting that pipe and cigar smoking constitute little danger to health appear to be inconsistent with the conclusion that tobacco per se is the prime deleterious factor. While the report places considerable emphasis on metaplastic and precancerous histologic changes in the tracheobronchial tree of smokers, the fact remains that the incidence of tracheal cancer has not increased with that of lung cancer, bilateral lung cancer (which would be expected) is rare, and the "precancerous" lesions present in patients who survive excision of a full-blown lung tumor do not generally go on to produce a second cancer. Since lung cancer appears to be highly age specific, occurring at about age 60 regardless of the age at which smoking was begun, dosage factors in terms of amount smoked or duration of smoking do not appear to be significant. The author concludes with the statement that "Without any idea of whitewashing the guilt that may rest at the feet of the tobacco habit, however practiced, and with a mind kept open for its possible incrimination, I cannot (in light of these many incongruities) consider it established as causative in cancer of the lung."</p>					
ABSTRACTOR	DATE	EDITOR	PROOFREAD	FINAL OK RRB	PREPARE DESCRIPTORS ON BACK SIDE OF THIS PAPER

Categories: 9

Descriptors

<u>Primary</u>	<u>Secondary</u>	<u>Tertiary</u>	<u>Quaternary</u>
SURGEON GENERAL'S REPORT HI	CIGAR SMOKING	LUNG CANCER MORTALITY	USA RESIDENCE
GOVERNMENT HEALTH ROLE HI	PIPE SMOKING	LARYNX CANCER MORBIDITY	ENGLISH LANGUAGE
LUNG CANCER TOBACCO CAUSATION 2	LUNG CANCER MORBIDITY	CIGARETTE CONSUMPTION	CHICAGO
CIGARETTE SMOKING	TRACHEA CANCER MORBIDITY	CHRONIC BRONCHITIS	
CIGARETTE TAXES	LIFE EXPECTANCY INCREASE	SMOKING MORBIDITY ASSOCIATION	
EDITORIAL	TRACHEA HISTOLOGY	LABELLING	
SURVEY STUDY HI	BRONCHUS HISTOLOGY	SEX DIFFERENCES	
	METAPLASIA	IRRITATION	
	AGE FACTORS		
	SMOKING DURATION		
	SMOKING AMOUNT		
	BILATERAL LUNG CANCER		
	TRACHEA CANCER TOBACCO CAUSATION 3		
	SMOKING NEGATIVE DOSE RESPONSE		
	PRECANCER HI		
	SECOND CANCERS		

PROJECT FILE		ACCESSION NUMBER		0308	
TITLE: Smoking and Mouth-Throat Cancer					
AUTHOR(S): Moore, C.					
SOURCE: Amer J Surg 108: 565-569, 1964					
AFFILIATION: U Louisville Sch Med, Louisville, Ky					
<p>ANNOTATION: A follow-up study of 78 previously cured patients showed that second cancers of the mouth and throat occurred at a much higher rate among those who continued to smoke (17 of 49) than among those who quit (1 of 29). It is strongly suggested "that tobacco is a determining factor in mouth-throat cancer, without which relatively few such cancers would develop", and that "a highly worthwhile degree of protection" results from stopping smoking. It is admitted, however, that "any serious concept of cancer causation must include a multitude of factors acting together, of which an external chemical agent can only be one."</p>					
<p>ABSTRACT: The appreciable frequency, especially in smokers, of often-fatal, new squamous carcinomas of the mouth-throat region several years after control of the first carcinoma prompted a follow-up study (mean follow-up of 6.7 years) of 78 patients (initially smokers) who were living and well 3 years following treatment for squamous cancer of the mouth or throat. The 78 subjects divided themselves into 2 groups: those who quit smoking following their first cancer (29 subjects), and those who continued smoking (49 subjects). Of the 29 who had quit, one person developed a second "tobacco-area squamous cancer", while 17 second cancers developed in the group who continued smoking. It is mentioned that 7 of an original group of 85 patients with oropharyngeal carcinomas had never smoked, so that "their cancers had causes other than tobacco", that "several" patients developed lower esophageal second cancers, which were not counted in the study, and that "the infrequency of cancer in certain oropharyngeal sites" makes statistical studies difficult. The author points out that in most studies, "the factors of innate susceptibility to cancer-----are not considered or equalized" and suggests that his two groups may have been "more homogeneous than an inbred strain of laboratory animals", while admitting that the patients may have varied widely with respect to race, alcoholic intake, diet, weight, previous syphilis, or some other factor which could account for the second cancer distribution. He also suggests "that tobacco may act as a promoter rather than a carcinogen per se," but points out that from a clinical standpoint "this is quibbling if the withholding of an external substance can control the major incidence of the disease." While maintaining that there is probably, in many cases, "a reversible precancerous state in the oral mucosa" which can be reversed by cessation of smoking, he admits that "the numbers of the subgroups are quite small and the number of uncontrolled variables in any human groupings necessarily numerous; therefore, few will consider the causal connection as proved."</p>					
ABTRACTOR	DATE	EDITOR	PROOFREAD	FINAL OK	PREPARE DESCRIPTORS ON BACK SIDE OF THIS PAPER
Dr. R.L. Pollack	11/17/66			RRB	

Category: 1

Descriptors

<u>Primary</u>	<u>Secondary</u>	<u>Tertiary</u>	<u>Quaternary</u>
SECOND CANCER MORBIDITY	SQUAMOUS CELL CARCINOMA	CIGARETTE SMOKING	USA RESIDENCE
MOUTH CANCER TOBACCO CAUSATION 1	OROPHARYNGEAL CARCINOMA CONCESSION	PIPE SMOKING	ENGLISH LANGUAGE
THROAT CANCER TOBACCO CAUSATION 1	NONSMOKERS	TOBACCO CHEWING	LOUISVILLE
TOBACCO SMOKING	ESOPHAGUS CARCINOMA	SNUFF DIPPING	LOUISVILLE GENERAL HOSPITAL
SMOKING DISCONTINUATION	STATISTICAL STUDIES CONCESSION	LARYNX CARCINOMA	PYRIFORM SINUS CANCER
EXSMOKERS	CONSTITUTIONAL FACTORS CONCESSION	BUCCAL FLOOR CARCINOMA	CIGAR SMOKING
PROSPECTIVE STUDY	CANCER SUSCEPTIBILITY	TONGUE CARCINOMA	LIP CANCER SUNLIGHT CAUSATION 2
HUNDRED	RACIAL FACTORS CONCESSION	PALATE CARCINOMA	SMOKING REDUCTION
CANCER CAUSATION CONCESSION	ALCOHOL CONSUMPTION CONCESSION	GINGIVA CARCINOMA	POLYCYCLIC HYDROCARBONS
CHEMICAL CARCINOGENESIS	DIETARY FACTORS CONCESSION	BUCCAL MUCOSA CARCINOMA	
	BODY WEIGHT CONCESSION	TONSIL CARCINOMA	
	SYPHILIS CONCESSION	LUNG CARCINOMA SMOKING CAUSATION 1	
	TOBACCO CARCINOGENICITY CONCESSION	PHARYNX CARCINOMA	
	TOBACCO PROMOTING ACTIVITY	MALE-FEMALE DATA	
	PRECANCER REVERSIBILITY	SMOKING AMOUNT	
	BUCCAL MUCOSA	SMOKING DURATION	
		ORAL CANCER MORBIDITY	
		THROAT CANCER MORBIDITY	
		MUCUS GLANDS	
		OROPHARYNGEAL EPITHELIUM	
		LARYNX EPITHELIUM	
		GENETIC FACTORS	
		VIRAL RESISTANCE	
		HORMONE IMBALANCE	
		LUNG MUCOSA	
		TISSUE SUSCEPTIBILITY	
		RADIATION	

ACCESSION NUMBER

TITLE: The anatomical approach to the study of smoking and bronchogenic carcinoma: A preliminary report of forty-one cases

AUTHOR(S): Auerbach, O. / Pedrick, T. G., Stout, A. P., Statsinger, A. L., Mehusam, G. E., Forman, J. B., Goss, L. B.

SOURCE: Cancer 9(1): 76-83, 1956

AFFILIATION: VA Hosp, Lab Svc, East Orange, N. J.

ANNOTATION: Epithelial changes in the tracheobronchial tree were studied in 41 specimens obtained from adult males, including 14 with bronchial carcinoma (all moderate or heavy smokers) and 27 without lung cancer (8 nonsmokers and 19 light to heavy smokers). There was significantly more basal cell hyperplasia in smokers than in nonsmokers, and slightly more stratification and squamous metaplasia. Due to the small number of specimens studied, however (one surgical and 40 at autopsy), the authors "do not feel justified in drawing any conclusions". They also admit a deficiency in recording the presence of change in the epithelia but not the extent of the change in the cells, and emphasize that "the only factor with which we have concerned ourselves is the smoking history".

ABSTRACT: A smoker was defined as someone who had smoked up to one package daily; a moderate smoker, one to 2 packages daily; and a heavy smoker, more than 2 packages daily. These patients had smoked for from one to 54 years, with the majority smoking for 10 or more years. Of an original 97 specimens, 56 were rejected because of extensive denudation caused by improper slide preparation technique. For the 41 remaining cases, approximately 7000 slides were studied and three types of epithelial change (basal-cell hyperplasia, stratification, and squamous metaplasia) were defined and evaluated. Basal-cell hyperplasia was present in 18%, 45%, 40%, and 42.7% of the sections, stratification was present in 1%, 7%, 10%, and 8.4% of the sections, and squamous metaplasia was present in 0.25%, 1.3%, 3.2%, and 2.0% of the sections from nonsmokers, light to moderate smokers, heavy smokers, and subjects with carcinoma of the lung, respectively. Basal-cell hyperplasia may occur in any part of the tracheobronchial tree with the response in nonsmokers being slight to advanced and showing a greater tendency to extend to the circumference of the wall of the cell; many-layered hyperplasia was found in smokers only. Incidence of stratification was not as apparent as that of basal-cell hyperplasia as "it was often associated with a suppurative process and could have been secondary to the inflammatory process...It does not completely explain the higher incidence in the smokers, particularly in those instances in which the changes were located in the trachea and major bronchi not associated with inflammation". Squamous metaplasia was also present to a greater extent in the smoker group; these changes occurred in the branch bronchi and were most often associated with an inflammatory process. The authors note that "our findings warrant a more extensive study along similar lines to determine whether these differences will hold in a much larger series". They also state: "We fully recognize that the present series does not include the

ABSTRACTOR	DATE	EDITOR	PROOFREAD	FINAL OK	PREPARE DESCRIPTORS ON BACK SIDE OF THIS PAPER
C. Klein	12-21-66			RRB	

Index: 1, 2
 crypts

Primary descriptors	Secondary descriptors	Tertiary descriptors	Quaternary descriptors
CIGARETTE SMOKING SMOKING DURATION SMOKING AMOUNT BASAL CELL HYPERPLASIA CIGARETTE SMOKING ASSOCIATION EPITHELIAL CELL STRATIFICATION CIGARETTE SMOKING ASSOCIATION SQUAMOUS METAPLASIA CIGARETTE SMOKING ASSOCIATION BRONCHUS CARCINOMA CIGARETTE SMOKING ASSOCIATION BRONCHUS HISTOLOGY TRACHEA HISTOLOGY FIFTY MALE DATA AUTOPSY STUDY BRONCHUS EPITHELIUM TRACHEA EPITHELIUM NONSMOKERS METHODOLOGY CONCESSION OTHER FACTORS CONCESSION	EPITHELIUM DEMINATION BRONCHUS INFLAMMATION BRONCHUS SUPPURATION LUNG CARCINOMA MANY LAYERED HYPERPLASIA BRANCH BRONCHUS AGE FACTORS CONCESSION SEX DIFFERENCES CONCESSION SLIDE PREPARATION	PHOTOMICROGRAPHY CILIATED EPITHELIUM HISTOLOGICAL STAINS KERATIN PEARL FORMATION INTERCELLULAR BRIDGING LUNG CANCER CHROME CAUSATION BILATERAL LUNG CHANGES LUNG SECTION PREPARATION TRACHEOBRONCHIAL DISSECTION	ENGLISH LANGUAGE GRANTOR AMERICAN CANCER SOCIETY GRANTOR CHAS. PFIZER CO. EAST ORANGE BROOKLYN USA RESIDENCE LUNG TUBERCULOSIS BRONCHIECTASIS FUNGUS INFECTION FORMALIN SMOKING HISTORY RELIABILITY QUESTIONNAIRES COLUMNAR CELLS GOBLET CELLS

tracheobronchial diseases from children, adolescents,
 or women. The influence of age and sex must neces-
 sarily be considered and included in further similar
 surveys. (Abstract from the Chas. Pfizer Co., Inc.,
 Brooklyn, N. Y. and from the American Cancer
 Society)

Continued on next page of abstract--